REMARKS

Claims 1-22 were pending. Claims 1, 10-12, 14, 16, 18, 20 and 22 have been canceled without prejudice as drawn to non-elected subject matter. Applicants reserve the right to pursue the subject matter of the canceled claims in one or more related applications. Claim 4 has been canceled and its subject matter incorporated into claim 2. Claims 5-7 have been amended to delete dependency on canceled claim 4. Claim 3 has been amended to be in independent form. Claims 13 and 15 have been amended to be dependent upon additional claims. Claims 2, 3, 5-9 and 15 have been amended to more particularly point out and distinctly claim that which Applicants regard as the invention. Specifically, Claims 2 and 3 have been amended to recite, *inter alia*, a transgenic mouse. Support for this amendment can be found in the specification, for example, at page 6, line 19. Claims 2, 3 and 5-7 have been amended to recite, *inter alia*, a disruption in a FHIT gene. Support for this amendment can be found in the specification at page 6, line 20 to page 7, line 5. Claim 2 has been amended to recite, *inter alia*, a transgenic mouse the genome of which contains a disruption of a FHIT gene. Support for this amendment can be found in the specification at page 16, lines 24-28. Claims 2, 3, 8 and 9 have been amended to recite, *inter alia*, a transgenic mouse the genome of which contains a disruption of a FHIT gene, or a transgenic mouse wherein said mouse is chimeric for a disruption of a FHIT gene, wherein said mouse, or FHIT +/- progeny of said mouse, respectively, has increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice, or displays increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice. Support for this amendment can be found in the specification at page 50, line 12 (susceptibility to sebaceous tumors), page 2, lines 22-23 (visceral tumors) and page 44, line 34 to page 45, page 11 (comparison of NMBA on tumor formation in FHIT +/- mice versus FHIT +/+ mice). Claim 5 has been amended to recite, *inter alia*, a transgenic mouse the genome of which contains a disruption of a FHIT gene, wherein said disruption of the FHIT gene is in both germline and somatic cells. Support for this amendment can be found in the specification at page 2, lines 21-22. Claim 15 has been amended to recite, *inter alia*, that a reduced rate of tumor formation is indicative of a therapeutic or prophylactic value. Support for this amendment can be found in the specification at page 3, lines 3-8, reciting the method of testing molecules for treating or preventing cancer. Claims 2, 3 and 9 have also been amended to correct grammatical errors.

None of the above-made amendments introduces new matter. Applicants respectfully request entry of the amendments made herein. Upon entry of the amendments herein, Claims 2, 3, 5-9, 13, 15, 17, 19 and 21 will be pending and under consideration.

The Rejections Under 35 U.S.C. § 112, First Paragraph, For Lack of Enablement, Should Be Withdrawn

Claims 2-9, 13, 15, 17, 19 and 21 of the present application have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for "any nonhuman mammal, any transgenic without a phenotype that differs from the wild-type or mice with a homozygous disruption in FHIT".

Specifically, the Examiner alleges that, with respect to Claims 2 and 3, the specification does not enable making a transgenic in any species other than mice. While not admitting the propriety of the rejection and in an effort to advance prosecution of the instant application, Applicants have amended Claims 2 and 3 to refer to a transgenic mouse rather than any nonhuman mammal. Accordingly, this rejection has been obviated and Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that, with respect to Claims 2-7, 13, 15, 17, 19 and 21, the specification does not enable a "transgenic without a phenotype as broadly claimed". Applicants respectfully disagree. First, Applicants note that Claims 2 and 3 have been amended to clarify that which Applicants regard as the invention. In particular, Claim 2 has been amended to recite a phenotype of increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice. This reflects the phenotype of a transgenic mouse whose genome contains a disruption of the FHIT gene. Applicants have amended Claim 3 to be in independent form. Claim 3 is now directed to a transgenic mouse which is chimeric for the disruption of the FHIT gene, and which can transmit the phenotype associated with FHIT gene disruption to later generations (and thus contains germ cells with the disrupted FHIT gene).

The Examiner argues that, as presently claimed, 2-7, 13, 15, 17, 19 and 21 would encompass transgenics displaying any phenotype including a wild-type phenotype, while the specification does not provide an enabled use for the transgenic without a predisposition for

developing tumors. Applicants point out that amended Claim 2 specifies that the mouse has a phenotype of increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice, or increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice. Amended Claim 3 specifies that the mouse can produce progeny with such phenotype associated with FHIT disruption. The chimeric mice of Claim 3 can be bred to obtain a new line of mice containing the disrupted FHIT gene, *i.e.*, transgenic mice whose genome contains a disruption of a FHIT gene, thereby transmitting the defective FHIT gene to offspring. *See* the specification at page 30, lines 6-7, and at page 44, lines 17-18.

The Examiner asserts that the phenotype of the transgenics, in general, is unpredictable due to factors such as position effects and unidentified control elements resulting in a lack of transgene expression or variable expression. Applicants note that the position effects discussed by the Examiner, and in the references cited by the Examiner, relate to effects of the location of the chromosomal integration, in situations where a transgene is inserted for overexpression or misexpression, and do not relate to insertion of a transgene for knocking out a gene at a specific locus. The present invention is directed to FHIT gene knockouts, by virtue of a termination codon in exon 5, and a knockout construct would not be subject to position effects. Accordingly, this rejection has been obviated and Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that, with respect to Claim 8, skin tumors has a broader scope than sebaceous tumors. While not admitting the propriety of the rejection and in an effort to advance prosecution of the instant application, Applicants have amended Claim 8 to recite, *inter alia*, a transgenic mouse characterized by a predisposition to visceral and sebaceous tumors. Accordingly, this rejection has been obviated and Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that, with respect to Claim 9, the specification does not define hypersensitivity to NMBA and the claim does not state the sensitivity being compared. For clarity and not for purposes of changing the scope of the claims, Applicants have amended Claims 2 and 9 by deleting the recitation of "hypersensitivity". Claims 2 and 9, as amended herein, recite, *inter alia*, a transgenic mouse which displays increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice. Accordingly, Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that, with respect to Claims 2-5, 7-9, 13, 15, 17, 19 and 21 and Claim 6, the specification does not enable transgenics having a homozygous FHIT disruption because the specification does not teach the phenotype of FHIT -/- mice. Applicants respectfully disagree. The specification describes the production of mice with a homozygous FHIT disruption (*see* Section 6.2, page 44, lines 8-32). It is clear from the specification that the inventors regard the phenotypes of FHIT +/- and -/- mice as similar, as tumors from +/- mice were shown not to express FHIT protein. See the specification at page 50, line 17. Mice that are FHIT -/- would also not express FHIT protein, but would be expected to be more susceptible to tumors than FHIT +/+ mice. The similarity of phenotypes is confirmed by the specification which describes both +/- and -/- mice as "fertile, long-lived and sensitive to carcinogen" and "will serve as useful models for carcinogen-induction of tumors of various organs". See the specification, at page 50, lines 24-26. Thus, the specification provides guidance to one of skill in the art to determine how to use FHIT -/- mice, which have a similar phenotype to FHIT +/- mice. Both mice have the phenotype of increased susceptibility to tumors. Accordingly, a transgenic having a homozygous FHIT disruption is enabled and Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that the specification does not enable a "transgenic that merely has cells that contain a disruption of the FHIT locus". The Examiner asserts that the claims would encompass cells, having a disruption in the FHIT gene, injected into an animal. The claims have been amended to clarify that the presently claimed transgenic mice 1) have a genome which contains a disruption of the FHIT gene (Claim 2), or 2) are chimeric for a disruption of the FHIT gene (Claim 3). Moreover, Claim 3, as amended, specifies that the chimeric mouse of Claim 3 has the ability to pass the phenotype of increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice to its progeny, and thus it must contain germ cells that contain a disrupted FHIT gene. The claims, as amended, are fully enabled by the specification. Accordingly, Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that the "comparison step in the method claims does not enable one of skill to determine which molecules are carcinogenic". The Examiner notes that an increased rate of tumor formation must be compared to an animal that did not receive the test molecule. Applicants respectfully point out that Claims 13 and 15, as filed, recite, in step (b), comparing the rate of tumor formation in the transgenic mouse with a control mouse of

the same genotype to which the molecule is not administered. Accordingly, Applicants respectfully request withdrawal of this rejection.

For the above reasons, the rejections of Claims 2-9, 13, 15, 17, 19 and 21 under 35 U.S.C. § 112, first paragraph for lack of enablement have been obviated and Applicants respectfully request that these rejections be withdrawn.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

Claims 2-9, 13, 15, 17, 19 and 21 of the present application have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner alleges that the term "locus" in the claims is indefinite. While not admitting the propriety of the rejection and in an effort to advance prosecution of the instant application, Applicants have amended Claims 2, 3 and 5-7 to recite the FHIT gene rather than the FHIT locus. Accordingly, this rejection has been obviated and Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that "an exon 5 coding region" does not make sense. While not admitting the propriety of the rejection and in an effort to advance prosecution of the instant application, Applicants have amended Claim 2 to recite "the exon 5 coding region". Accordingly, this rejection has been obviated and Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that the phrase "being characterized by a predisposition to developing a spectrum of visceral and skin tumors" is unclear. The Examiner further alleges that "predisposition" is misspelled, and that the metes and bounds of "spectrum" and "characterized" cannot be determined. While not admitting the propriety of the rejection and in an effort to advance prosecution of the instant application, Applicants have amended Claims 2 and 3 by deleting the terms to which the Examiner objects. The amended claims recite "increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice". Accordingly, this rejection has been obviated and Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that the metes and bounds of "hypersensitivity" and "characterized" in the phrase "being characterized by a hypersensitivity to NMBA" cannot be determined. With respect to the term "characterized", Applicants have removed this term. With respect to "hypersensitivity", Applicants have removed this term and amended Claims 2 and 9 to recite a transgenic mouse which displays increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice. Claim 3, as amended, recites a chimeric mouse which displays increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice. Accordingly, Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that the phrases "wherein an increased rate of tumor formation following administration of the test molecule is indicative" and "wherein a reduced rate of tumor formation following administration of the test molecule is indicative" are incomplete because there is no comparison to a control. The Examiner notes that a different rate can only be determined when compared to a control that did not receive the test compound. Applicants respectfully point out that the claims containing these phrases, *i.e.*, Claims 13 and 15, respectively, do contain a comparison step (step b) where the rate of tumor formation of a transgenic mouse is compared to a control mouse of the same genotype to which the molecule is not administered. Accordingly, Applicants respectfully request that the rejection be withdrawn.

For the above reasons, the rejections of Claims 2-9, 13, 15, 17, 19 and 21 under 35 U.S.C. § 112, second paragraph have been obviated and Applicants respectfully request that the rejection be withdrawn.

The Rejection under 35 U.S.C. § 103 Should Be Withdrawn

Claims 2-5, 7, 13, 15, 17, 19 and 21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Capecchi (Scientific American, 1998, 270:34-41) in view of Julius (U.S. Patent 5,698,766) in view of Pekarsky (1998, Cancer Res. 58:3409-3414). Applicants respectfully disagree.

The Examiner states that Capecchi teaches making a HoxA-3 knockout mouse, a model for DiGeorge syndrome, but that Capecchi does not teach disruption of the FHIT gene.

The Examiner states that Pekarsky teaches the nucleic acid sequence of the mouse FHIT gene and that FHIT protein is lost in many cancer cells due to disruptions in the FHIT gene.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in a gene as taught by Capecchi wherein the gene is the FHIT gene as taught by Pekarsky. The Examiner asserts that one of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the FHIT gene in a transgenic mouse to determine the function of FHIT *in vivo*. The Examiner further asserts that motivation is provided by Capecchi by stating that other diseases can be studied by transgenesis and that mouse models are useful to understanding the functions of genes and make it possible to determine drugs that affect gene regulation. The Examiner states that Capecchi and Pekarsky do not teach inserting stop codons into exon 5 of the FHIT gene.

The Examiner states that Julius teaches a transgenic mouse having a disruption in exon 5 of the 5HT-2C receptor gene, by inserting stop codons.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to disrupt the FHIT gene as taught by Capecchi and Pekarsky wherein the disruption is caused by inserting stop codons into exon 5 as taught by Julius. The Examiner asserts motivation is provided because Pekarsky taught exon 5 was the beginning of the FHIT coding region.

The Legal Standard

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143.
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> "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).
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> The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Claim 2, as amended, is drawn, *inter alia*, to a transgenic mouse the genome of which contains a disruption of a FHIT gene, wherein said disruption comprises a termination codon in an exon 5 coding region, and wherein said mouse has increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or displays increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice. Claim 3, as amended, is drawn, *inter alia*, to a transgenic mouse wherein said mouse is chimeric for a disruption of the FHIT gene, wherein said disruption comprises a termination codon in an exon 5 coding region, and wherein FHIT +/- progeny of said mouse have increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or display increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice.

The cited references do not provide the requisite suggestion or motivation. Capecchi teaches making a HoxA-3 knockout mouse. Capecchi also teaches chimeric mice (which contain cells from two mouse strains). Capecchi does not mention the FHIT gene or suggest disrupting the FHIT gene in an exon 5 coding region, nor does it provide any indication of the phenotype of a FHIT knockout mouse or of a chimeric mouse that can provide such a phenotype to its progeny. Thus, Capecchi does not teach or suggest a transgenic mouse whose genome contains a disruption of the FHIT gene, wherein the disruption is in an exon 5 coding region and said mouse has increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or displays increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice, nor does Capecchi teach a transgenic mouse which is chimeric for the disruption of the FHIT gene, wherein the disruption is in an exon 5 coding region and wherein FHIT +/- progeny of said transgenic mouse have increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or display increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice.

Pekarsky does not remedy the deficiencies of Capecchi. Pekarsky teaches the nucleic acid sequence of the mouse FHIT gene and that FHIT protein is lost in many cancer cells due to disruptions in the FHIT gene. Pekarsky does not teach disrupting the FHIT gene in a transgenic mouse, nor does it suggest disrupting the FHIT in an exon 5 coding region, let

alone predict what phenotype such a mouse, chimeric or otherwise, or its progeny would have. Nor does it teach or suggest a chimeric mouse that can provide such a phenotype to its progeny. Thus, Pekarsky, either alone or in combination with Capecchi, does not teach a transgenic mouse whose genome contains a disruption of the FHIT gene, wherein the disruption is in an exon 5 coding region and said mouse has increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or displays increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice nor does Pekarsky teach a transgenic mouse which is chimeric for the disruption of the FHIT gene, wherein the disruption is in an exon 5 coding region and wherein FHIT +/- progeny of said transgenic mouse have increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or display increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice.

Julius does not remedy the deficiencies of Capecchi or Pekarsky. Julius teaches a transgenic mouse having a disruption in exon 5 of the 5HT-2C receptor gene, by inserting stop codons. Exon 5 of the 5HT-2C receptor gene is the fifth putative transmembrane segment of the receptor. See Julius, col. 6 lines 14-19. Exon 5 of the FHIT gene is the first coding region of the gene. Thus, because of the nonanalogous structures of genes, a teaching to introduce stop codons in exon 5 of one gene does not provide a teaching to introduce stop codons in exon 5 of another gene. Moreover, Julius does not even mention the FHIT gene, nor provide any suggestion of a phenotype of a transgenic mouse, chimeric or otherwise, containing a disruption of the FHIT gene. Nor does it teach or suggest a chimeric mouse that can provide such a phenotype to its progeny. Thus, Julius, either alone or in combination with Capecchi and Pekarsky, does not teach or suggest a transgenic mouse whose genome contains a disruption of the FHIT gene, wherein the disruption is in an exon 5 coding region and said mouse has increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or displays increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice nor does Julius teach a transgenic mouse which is chimeric for the disruption of the FHIT gene, wherein the disruption is in an exon 5 coding region and wherein FHIT +/- progeny of said transgenic mouse have increased susceptibility to visceral and sebaceous tumors relative to FHIT +/+ mice or display increased tumor formation upon being exposed to NMBA relative to FHIT +/+ mice.

For the reasons discussed above, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants respectfully request that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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